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### **REMARKS**

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited.

### A. Related Applications

The Applicants wish to draw the Examiner's attention to the existence of Applicants' related cases directed to nanoparticle-based compositions, methods of making, and methods of use. Many of these cases have received Office actions and a number of these cases have already issued. These cases are listed in Appendix A (attached).

## B. Amendments to the specification

The specification was amended to update the priority claim as well as to correct for a typographical error. No new matter has been added to the application as a result of the present amendment.

### C. Amendments to the claims

Claims 434, 436-452, 454-464 and 485 were pending in this case. Claim 445 was amended and new claims 487 and 488 were added. Support for the amendments and new claims can be found in the specification, for instance, at page 31, lines 18 and 19 and Figures 45 and 46. Accordingly, no new matter has been added to the application as a result of the present amendment.

#### D. Information Disclosure Statements

The Applicants note that the Examiner did not return an executed copy of the PTO 1449 forms for the Information disclosure statement and 5<sup>th</sup> Supp. Information disclosure statement, both hand delivered to the Examiner on January 15, 2004. Based on the undersigned representative's review of the public PAIR system, these two statements, references and PTO 1440 forms were stamped as received by the Patent Office on January 15, 2004. The Applicants request that the Examiner execute the attached copies of the PTO 1449 forms and return a copy of the same to the undersigned representative.

## E. Rejection under 35 U.S.C. section 102(b) based on Hainfeld

Claim 434 stands rejected under 35 U.S.C. section 102(b) as being anticipated by Hainfeld (U.S. Patent No. 5,521,289). Specifically, the Examiner alleges that the invention of claim 434 is old because Hainfeld allegedly disclosed organothiol metal cluster compounds. The Applicants respectfully traverse this rejection.

As a threshold matter, the Federal Circuit has stated that for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Coming Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983). Contrary to the Examiner's position, Hainfeld does not disclose the presently claimed invention.

Hainfeld relates to small organometallic probes. While Hainfeld does describe organothiol metal clusters that include organothiols, Hainfeld is completely silent with respect to nanoparticle conjugates having a covalently bound polythiol functional group. See claim 434. Accordingly, Hainfeld does not anticipate claim 434. Withdrawal of this section 102(b) rejection against claim 434 based on Hainfeld is in order and is respectfully requested.

## F. Rejection under 35 U.S.C. section 102(e) based on Leone

Claim 434 also stands rejected under 35 U.S.C. section 102(e) as being anticipated by Leone et al (U.S. Patent No. 6,369,206) ("Leone"). Specifically, the Examiner alleged that the invention of claim 434 is old because Leone allegedly disclosed metal organothiol particles, cited to col. 11. Applicants respectfully traverse this rejection and submit that Leone does not disclose or suggest the presently claimed invention.

Leone relates to metal organothiol particles. While Leone does describe organothiol metal clusters that include organothiols, Leone is completely <u>silent</u> with respect to nanoparticle conjugates having a covalently bound <u>polythiol</u> functional group. See claim 434. Accordingly, Leone does not anticipate claim 434. Withdrawal of this section 102(b) rejection of claim 434 based on Leone is in order and is respectfully requested.

# G. Rejection under 35 U.S.C. sections 102(e)/103

Claims 434, 436-452, 454-464, and 485 stand rejected as anticipated by or, in the alternative, under 35 U.S.C. section 103(a) as obvious over Yguerabide et al. (U.S. Patent No. 6,214,560)("Yguerabide"). The Examiner's detailed comments can be found on pages 5-7 of the office action. Applicants respectfully traverse.

The Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." In re Vaeck, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1485 (Fed. Cir. 1991), citing In re Dow Chemical Co., 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). Contrary to the Examiner's position, the Applicants submit that Yguerabide does not teach or suggest what the Applicants have done.

The present invention is directed to nanoparticle-oligonucleotide probes comprising nanoparticles having oligonucleotides bound thereto, wherein each of the oligonucleotides has a covalently bound polythiol functional group that can bind to the nanoparticles. Previously, nanoparticle conjugates were prepared using conventional alkylthiol (RSH) or acyclic disulfide (RS-SR) and the resulting probes are quite sensitive to thiol cleaving reagents such as DTT which is present in many assay buffer solutions. The inventors have developed nanoparticle-oligonucleotides probes from oligonucleotides having covalently bound polythiol functional groups. The resulting probes have a surprising and unexpected enhanced stability towards such thiol cleaving reagents such as dithiothreitol (DTT). Example 25 (page 156 to 158 of the specification) includes a side-by-side comparison of three nanoparticle oligonucleotide probes prepared with oligonucleotides having covalently bound single thiols, cyclic disulfides, or a polythiol (e.g., trithiol). As discussed in this Example, DTT displaces the oligonucleotides from the probes, thereby enabling the gold nanoparticles to aggregate and exhibit a characteristic change in color from red to blue. The DTT displacement time was 1.5 hours (single thiol), 20

hours (cyclic disulfide) and 40 (polythiol) for these probes, demonstrating the unusual stability of nanoparticle-oligonucleotide probes prepared with oligonucleotides having covalently bound polythiol functional groups.

The Examiner alleged that the presently claimed invention is anticipated or obvious in that Yguerabide disclosed a detection method and gold particulate labels for the detection of analytes in a sample. With respect to a method of specific detection of one or more analytes in a sample, Yguerabide described a method of detection based on illumination and light scattering. See Yguerabide at col. 73 and 74. Col. 83 provides further discussion regarding particle size and particle binding to a surface. Cols. 77-80 relate to particles and their preparation. However, contrary to the Examiner's position, Yguerabide is completely silent with respect to any to nanoparticle conjugates having a covalently bound polythiol functional group and method for preparation of such conjugates.

The Examiner also alleged that Yguerabide taught detection and measurement of one or more analytes in a sample using gold particulate labeled probes and that the recited surface density is obvious. However, with respect to surface density, Yguerabide in col. 82, line 35, merely discusses surface density of the number of particles present in a spot on a substrate. Mere disclosure of particle density on a surface of a substrate is not a disclosure of oligonucleotide density on a surface of a particle. Col. 83 provides further discussion regarding particle size and particle binding to a surface. Cols. 77-80 relate to particles and their preparation. Col. 110 (Example 32) relates to a nucleic acid labeled particle but does not provide or suggest any particle surface density. Indeed, no particle surface density can be calculated from Yguerabide's disclosure since he does not provide any DNA concentrations that are necessary to calculate surface density. Thus, Yguerabide is completely silent with respect to any particle having oligonucleotides with the surface density recited in the present claims 433. Yguerabide cannot be relied on to support a section 102(e) or 103(a) rejection of the present claims.

Furthermore, the Examiner alleged that the recitations "recognition oligonucleotides" and "spacer portion" are overly broad and would encompass any nucleotide sequence. However, as described in the specification, "recognition oligonucleotides" refers to oligonucleotides which comprise a "sequence complementary to at least a portion of the sequence of a nucleic acid or oligonucleotide target." See page 79, lines 28-30. The "spacer portions" of the recognition

oligonucleotides allows for binding of the recognition oligonucleotides onto nanoparticles and for spacing away of the recognition portion of the recognition oligonucleotides away from the nanoparticle surface so that the recognition portion is more accessible for hybridization with a target. See page 80, lines 1-12. As discussed in the specification, the spacer portion may have any sequence which "does not interfere with the ability of the recognition oligonucleotides to become bound to the nanoparticles or to a nucleic acid or oligonucleotide target." See page 80, lines 12-17.

In light of the teachings in the specification, a person of ordinary skill in the art would appreciate that recognition oligonucleotides and spacer portions are not overly broad in their scope. Moreover, there is no discussion or suggestion anywhere in Yguerabide of any nanoparticle comprising recognition and spacer portions of recognition oligonucleotides as presently claimed.

In summary, the present claims recite limitations that are neither taught, made obvious, or suggested by the cited reference. Thus, the Applicant respectfully submits that Yguerabide cannot be applied to support section 102(e) and/or section 103(a) rejections of the claims. Withdrawal of these rejections is in order and is respectfully requested.

#### H. Conclusion

In light of the above amendment and discussion, the Applicants submit that the claims are in condition for an allowance. Notice to this effect is in order and is respectfully requested.

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the undersigned representative if the Examiner believes that this would be helpful in expediting the prosecution of this application.

Respectfully submitted,

Dated: Lpt. 22, 200

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Telephone: 312-913-0001 Facsimile: 312-913-0002

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# APPENDIX A

ATTY	Serial No.		
Case No.	Filing Date	Inventors/Title	Status
00-1085-A	USSN 09/820,279		Granted as US Pat.
]	Filed 03/28/01	MATERIALS FOR ASSAYING	No. 6,750,016
		BIOLOGICAL MATERIALS	Issued 06/15/04
00-1085-G	USSN 10/640,618	See 00-1085-A	Allowed
	Filed 08/13/03		
00-1086-A	USSN 09/903,461	Letsinger, et al. / METHOD OF	Granted as US Pat.
	Filed 07/11/01	DETECTION BY ENHANCEMENT	No. 6,602,669
		OF SILVER STAINING	Issued 8/5/03
00-1124-A	USSN 09/998,936	Mirkin, et al. / SILVER STAINING	Granted as US Pat.
	Filed 11/30/01	REMOVAL BY CHEMICAL	No. 6,726,847
		ETCHING AND SONICATION	Issued 04/27/04
00-1272-C	USSN 10/008,978	Mirkin, et al. / NANOPARTICLES	Granted as US Pat.
}	Filed 12/7/01	HAVING OLIGONUCLEOTIDES	No. 6,984,491
		ATTACHED THERETO AND USES	Issued 01/10/06
		THEREFOR	
00-1272-F	USSN 11/050,983	See 00-1272-C	Pending
	Filed 02/04/05		
00-653-G	USSN 10/794,741	Mirkin, et al. / NANOPARTICLES	Pending
	Filed 03/05/04	HAVING OLIGONUCLEOTIDES	
		ATTACHED THERETO AND USES	}
		THEREFOR	
00-713-B1	USSN 09/923,625	Mirkin, et al. / NANOPARTICLES	Granted as US Pat.
	Filed 08/07/01	HAVING OLIGONUCLEOTIDES	No. 6,773,884
		ATTACHED THERETO AND USES	Issued 08/10/04
		THEREFOR	
00-713-C	USSN 09/344,667	See 00-713-B1	Granted as US Pat.
	Filed 06/25/99		No. 6,361,944
			Issued 03/26/02
00-713-I	USSN 09/603,830	See 00-713-B1	Granted as US Pat.
	Filed 06/26/00		No. 6,506,564
00 = = = = =	770.00.00.00.00		Issued 01/14/03
00-713-I-1	USSN 09/961,949	See 00-713-B1	Granted as US Pat.
	Filed 09/20/01		No. 6,582,921
00 T10 T 10			Issued 06/24/03
00-713-I-10	USSN 09/973,788	See 00-713-I-1	Granted as US Pat.
	Filed 10/10/01		No. 6,720,411
00 512 7 7 7	77007700000		Issued 04/13/04
00-713-I-11	USSN 09/975,062	See 00-713-I-1	Granted as US Pat.
	Filed 10/11/01	•	No. 6,677,122
00 710 7 75	77007 40 45 55 55	·	Issued 01/13/04
00-713-I-13	USSN 09/975,384	See 00-713-I-1	U.S. Patent No.

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A TOTAL Z	Serial No./		Page 2 of 5
ATTY	I	I/Fi4lo	Status
Case No.	Filing Date Filed 10/11/01	Inventors/Title	7,098,320
		0 - 00 712 11	Granted as US Pat.
00-713-I-14	USSN 09/975,498	See 00-713-I-1	_
	Filed 10/11/01		No. 6,861,221
			Issued 03/01/05
00-713-I-15	USSN 09/975,059	See 00-713-I-1	Granted as US Pat.
ŀ	Filed 11/11/01		No. 6,828,432
			Issued 12/07/04
00-713-I-16	USSN 09/976,601	See 00-713-I-1	Granted as US Pat.
	Filed 10/12/01		No. 6,903,207
			Issued 07/0 <u>7/0</u> 5
00-713-I-17	USSN 09/976,968	See 00-713-I-1	Granted as US Pat.
	Filed 10/12/01		No. 6,818,753
	ļ.		Issued 11/ <u>16/0</u> 4
00-713-I-18	USSN 09/976,971	See 00-713-I-1	Granted as US Pat.
	Filed 10/12/01		No. 6,682,895
			Issued 01/27/04
00-713-I-19	USSN 09/976,863	See 00-713-I-1	Granted as US Pat.
	Filed 10/12/01		No. 6,986,989
			Issued 01/17/06
00-713-I-2	USSN 09/957,318	See 00-713-I-1	Granted as US Pat.
	Filed 09/20/01		No. 6,759,199
		- -	Issued 07/06/04
00-713-I-20	USSN 09/976,577	See 00-713-I-1	Granted as US Pat.
** **	Filed 10/12/01		No. 6,720,147
		i	Issued 04/13/04
00-713-I-21	USSN 09/976,618	See 00-713-I-1	Granted as US Pat.
** .=* = ==	Filed 10/12/01		No. 6,812,334
			Issued 11/02/04
00-713-I-22	USSN 09/981,344	See 00-713-I-1	Granted as US Pat.
	Filed 10/15/01		No. 6,777,186
	A 10-4- A 31 M41 V 2		Issued 08/17/04
00-713-I-23	USSN 09/976,900	See 00-713-I-1	Granted as US Pat.
	Filed 10/12/01		No. 6,902,895
			Issued 06/07/05
00-713-I-24	USSN 09/976,617	See 00-713-I-1	Granted as US Pat.
00 /10 1 2 1	Filed 10/12/01		No. 6,730,269
			Issued 05/04/04
00-713-I-25	USSN 09/976,378	See 00-713-I-1	Granted as US Pat.
	Filed 10/12/01		No. 6,969,761
			Issued 11/29/05
00-713-I-26	USSN 10/410,324	See 00-713-I-1	Granted as US Pat.
VV , I.J-I-MU	Filed 04/10/03		No. 6,962,786
	7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7		Issued 11/08/05
00-713-I-3	USSN 09/957,313	See 00-713-I-1	Granted as US Pat.
00-113-1-3	בוב, ו כקובט אופפט	200 00-113-1-1	Granica as OS Fat.

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ATTY	Serial No./		04444
Case No.	Filing Date	Inventors/Title	Status
	Filed 09/20/01		No. 6,645,721
			Issued 11/11/03
00-713-I-4	USSN 09/966,491	See 00-713-I-1	Granted as US Pat.
	Filed 09/28/01		No. 6,610,491
_			Issued 08/26/03
00-713-I-5	USSN 09/966,312	See 00-713-I-1	Granted as US Pat.
	Filed 09/28/01		No. 6,673,548
			Issued 01/06/04
00-713-I-6	USSN 09/967,409	See 00-713-I-1	Granted as US Pat.
	Filed 09/28/01		No. 6,740,491
			Issued 05/24/04
00-713-I-7	USSN 09/974,500	See 00-713-I-1	Granted as US Pat.
00 .10 1 .	Filed 10/10/01		No. 6,709,825
	10.10.0		Issued 03/23/04
00-713-I-8	USSN 09/974,007	See 00-713-I-1	Allowed
00-715-1-0	Filed 10/10/01		
00-713-I-9	USSN 09/973,638	See 00-713-I-1	Granted as US Pat.
00-713-1-9	Filed 10/10/01	BCC 00-713-1-1	No. 6,878,814
	riied 10/10/01		Issued 04/12/05
00-713-L	USSN 09/693,005	See 00-713-B1	Granted as US Pat.
00-/13-L	Filed 10/20/00	3ee 00-713-B1	No. 6,495,324
	F11ed 10/20/00		Issued 12/17/02
00 510 74	TIGG21 00/602 262	6 00 712 D1	Granted as US Pat.
00-713-M	USSN 09/693,352	See 00-713-B1	
	Filed 10/20/00		No. 6,417,340
			Issued 07/09/02
00-714-G	USSN 09/830,620	Mirkin, et al. / NANOPARTICLES	Allowed
	Filed 8/15/01	WITH POLYMER SHELLS	770 7
00-715-A	USSN 09/760,500	Mirkin, et al. / NANOPARTICLES	Granted as US Pat.
	Filed 01/12/01	HAVING OLIGONUCLEOTIDES	No. 6,767,702
		ATTACHED THERETO AND USES	Issued 07/27/04
		THEREFOR	
00-715-B	USSN 10/716,829	See 00-715-A	Pending
	Filed 11/18/03		
01-1565-A	USSN 10/266,983	Park, et al. / NANOPARTICLES	Allowed
	Filed 10/08/02	HAVING OLIGONUCLEOTIDES	
		ATTACHED THERETO AND USES	
		THEREFOR	
01-1633-A	USSN 10/612,422	Storhoff, et al. / NANOPARICLE	Pending
_	Filed 07/02/03	POLYANION CONJUGATES AND	_
		METHOD OF USE THEREOF IN	
		DETECTING ANALYTES	
01-1705-A	USSN 10/108,211	Mirkin, et al. / BIO-BARCODES	Granted as US Pat.
	Filed 03/27/02	BASED ON OLIGONUCLEOTIDE-	No. 6,974,669
	- 1100 00:01/00	MODIFIED NANOPARTICLES	Issued 12/13/05

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ATTY	Serial No./		<b>.</b>
Case No.	Filing Date	Inventors/Title	Status
01-1705-F	USSN 11/217,106	See 01-1705-A	Pending
	Filed 08/31/05		
01-565-A	USSN 10/125,194	Mirkin, et al. / DNA-BLOCK	Pending
	Filed 04/18/02	COPOLYMER CONJUGATES	
01-599-A	USSN 10/291,291	Garimella, et al. / BIOCONJUGATE-	Pending
	Filed 11/08/02	NANOPARTICLE PROBES	
01-661-A	USSN 10/034,451	Mirkin, et al. / DNA-MODIFIED	Allowed
	Filed 12/28/01	CORE-SHELL AG/AU	
		NANOCRYSTALS	
01-661-C	USSN 10/153,483	See 01-661-A	Allowed
	Filed 05/22/02		
01-661-E	USSN 10/397,579	See 01-661-A	Allowed
	Filed 3/26/03		1
01-801-A	USSN 10/210,959	Cork, et al. / NANOPARTICLE	Pending
	Filed 08/02/02	IMAGING SYSTEM	- 40
01-897-B	10/194,138	Garimella, et al. / METHOD FOR	Pending
	Filed 07/12/02	IMMOBILIZING MOLECULES	
		ONTO SURFACES	
02-035-C	USSN 10/352,714	Patno, et al. / HYBRIDIZATION	Pending
	Filed 01/27/03	DEVICE AND METHOD	
02-1227-A	USSN 10/735,357	Bao, et al. / DIRECT SNP	Pending
	Filed 12/12/03	DETECTION WITH UNAMPLIFIED	
		DNA	
02-307-A	USSN 10/437,753	Patno, et al. / MICROFABRICATED	Pending
	Filed 05/14/03	ELECTRODE ARRAY CHIP FOR	
		ELECTRICAL DETECTION OF	
	770077 4 0 4 4 4 7 0 7 0	DNA HYBRIDIZATION	7 1
02-334-A	USSN 10/447,073	Garimella, et al. / METHOD FOR	Pending
	Filed 05/28/03	PREPARING SUBSTRATES	
		HAVING IMMOBILIZED	
	TT007111101 600	MOLECULES AND SUBSTRATES	73 - 11 - 1
02-334-B	USSN 11/124,609	See 02-334-A	Pending
00 000 T	Filed 05/06/05	A CONTRACT OF THE PROPERTY OF	Donations
02-338-B	USSN 10/172,428	Mirkin, et al. / MULTICHANNEL	Pending
	Filed 06/14/02	DETECTION USING	
		NANOPARTICLE PROBES WITH	
		RAMAN SPECTROSCOPIC FINGERPRINTS	
02-338-C	USSN 10/431,341	See 02-338-B	Pending
U4-336-L	Filed 05/07/03	DCC 02-330-D	Y curing
02 214 4		Dag et al /I ADRI EDDE CENTE	Pending
03-214-A	USSN 10/789,831	Bao, et al. / LABEL-FREE GENE EXPRESSION PROFILING WITH	Lemik
	Filed 02/27/04	UNIVERSAL NANOPARTICLE	
		PROBES IN MICROARRAY ASSAY	
	<u> </u>	I RODES IN MICKUARRAI ASSAI	

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ATTY Case No.	Serial No./ Filing Date	Inventors/Title FORMAT	Status
03-466-C	USSN 10/854,848 Filed 05/27/04	Storhoff, et al. / METHOD FOR DETECTING ANALYTES BASED ON EVANESCENT ILLUMINATION AND SCATTER- BASED DETECTION OF NANOPARTICLE PROBE COMPLEXES	Pending
03-466-E	USSN 10/995,051 Filed 11/22/04	See 03-466-C	Pending
03-666-Е	USSN 10/877,750 Filed 06/25/04	Mirkin, et al. / BIO-BARCODE BASED DETECTION OF TARGET ANALYTES	Pending
03-666-G	USSN 11/127,808 Filed 05/12/05	See 03-666-E	Pending
04-060-A	USSN 11/121,165. Filed 05/03/05	Muller, et al. / APTAMER- NANOPARTICLE CONJUGATES AND METHOD OF USE FOR TARGET ANALYTE DETECTION	Pending
04-437-A	USSN 11/189,546 Filed 07/26/05	Ramakrishnan, et al. / METHOD FOR DISTINGUISHING METHICILLIN RESISTANT S. AUREUS FROM METHICILLIN SENSITIVE S. AUREUS IN A MIXED CULTURE	Pending